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RESEARCH ARTICLE

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Granulocyte-colony stimulating factor administration among hemoglobin S trait donors: A single center experience from the Eastern Mediterranean region

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Abstract

Background and Objective: Assessment of Hemoglobin S trait donors has gained importance together with the increased allogeneic peripheral stem cell transplant activity for sickle cell disease in the regions where the disease is prevalent. Outcomes of Granulocyte-Colony Stimulating Factor (G-CSF) administration are obscure for hemoglobin S trait donors. This study aims at investigating the incidence of hemoglobin S carrier status and outcomes of G-CSF administration among donors who live in Eastern Mediterranean region.

Material and Method: The cross-sectional, single-center cohort study was performed with 147 donors between January 2013 and March 2017. Prevalence of hemoglobin S trait was estimated and subjects with or without Hemogobin S trait were compared with regard to stem cell characteristics, early and late clinical outcomes after G-CSF administration.

Results: Eleven out of 147 donors (7.48%) were found as hemoglobin S trait. G-CSF administration was successfully completed and yielded good harvesting results in hemoglobin S trait donors. No statistically significant difference was found between groups with regard to early and late side effects, stem cell characteristics. Blood pressures and QTc values were within normal ranges in both groups. Groups were similar with regard to CD34 values.

Conclusion: G-CSF seems safe in hemoglobin S trait donors. Their being eligible as donors would increase the chance of the patients for allogeneic stem cell transplantation in high prevalence regions. Further studies are required to reveal the safety profile of G-SCF in hemoglobin S carriers in different regions.

KEYWORDS
G-CSF, hemoglobin S trait donor, sickle cell disease, stem cell mobilization

1 | INTRODUCTION

Allogeneic peripheral stem cell transplant activity from related or unrelated donors has increased in recent years. The hematopoietic stem cell product is the most critical material used for these transplants. Another option for the patients who do not have a matched donor is applying to bone marrow banks which have volunteer donors. A huge number of volunteer unrelated donors are available.[1] Approximately 28 million volunteers from 55 countries are available in the registry of World Bone Marrow Donor Association and 12 000 transplants are performed yearly from these donors.[2] >30 000 transplants have been performed from unrelated donors registered in the National Bone Marrow Donor

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Program (NMDP).[3] The target of the Turkish Stem Cell Coordination Center is to reach 500 000 volunteer donors.[4] The date September 17th is celebrated as the "World Marrow Donor Day" by NMDP every year for remembering and thanksgiving for this great contribution of donors. Subsequently, donor safety issues arise from these huge numbers. The European Union directives 2004/23/EC, the commission directives 2006/17/EC, 2006/86/EC and international standards emphasize the importance of donor safety and specify some rules. International standards such as FACT-JACIE and Netcord-FACT demand provision of donor convenience following donor selection and assessment procedures performed in accordance with standards.

Sickle cell disease (SCD) is the most common single gene disease worldwide. The heterozygous trait (sickle cell trait) is common among Afro-Americans, Asians, Indians, Latin Americans, Mediterranean, and Middle East communities.[5,6] Individuals with sickle cell trait are suggested to be susceptible to health-related problems such as venous thrombosis, cardiovascular diseases, sudden death, and rhabdomyolysis despite hematological parameters being within normal ranges.[7–11] Some of the healthy volunteers are naturally anticipated to be hemoglobin S trait, particularly in the above mentioned regions. The number of allogeneic hematopoietic stem cell transplants (HSCT) from related donors using stem cells from peripheral blood is also gradually increasing among adult SCD patients who may have a hemoglobin S trait-related donor.[12] According to EBMT CIBMTR 1986–2013 data, a total of 154 adult transplants were performed for SCD worldwide. While stem cell source was bone marrow for 111 of them, peripheral stem cell was used for the remaining 44. This condition requires care for safety issues for the hemoglobin S trait donors who are mobilized using granulocyte-colony stimulating factor (G-CSF).

The outcomes of G-CSF administration are obscure for hemoglobin S carrier donors. While some studies indicate that it may precipitate painful crises and life-threatening organ damage independently from the leukocyte count, some others indicate that it is safe.[13,14] Hemoglobin S status could show phenotypical variability among races. This study aims at investigating the incidence of hemoglobin S trait status and the outcomes of G-CSF administration in a homogenous ethnic group who live in the Eastern Mediterranean region where hemoglobinopathy is prevalent.

2 | MATERIAL AND METHOD

2.1 | Study plan

The study was a cross-sectional, single-center cohort study performed between January 2013 and March 2017. Safety problems were investigated in stem cell donors who underwent mobilization using G-CSF.

A total of 147 donors were selected in accordance with the standard operating procedure for donor selection and assessment (SOP: KIT-kU-003), and the frequency of hemoglobin S trait donors was determined. Eleven consecutive hemoglobin S trait donors with a mean age of 36.0 ± 15.2 (range 10–57) years constituted Group 1. The control group (Group 2) was composed of 136 consecutive healthy donors aged between 9 and 58 years. The groups were compared with regard to the early and late side effects of G-CSF. The donor follow-up procedure was performed on the subjects in both groups in accordance with the standard operating procedure for donor follow-up. Donors were invited for controls on Week 1, and year 1 after stem cell collection; physical examinations; and complete blood count were performed.

The primary endpoints included early severe adverse events and side effects developing within 30 days following the mobilization and collecting procedures. The secondary endpoints included the late severe adverse events and side effects developing between 30 days and one year after the procedure. Adverse events or side effects which had led to death, permanent disability, and prolonged hospitalization were evaluated as "severe."

A special recording system which meets the JACIE standards (Nucleus version 9.3.39; Monad software, Ankara), which uses the international terminology criteria (CTCAE version 4.0) was used for recording the adverse events and side effects that are encountered during the mobilization procedure using G-CSF. The data were checked by a data audit group.

Subjects who did not meet the donor eligibility criteria due to medical history, serological tests, co-morbid conditions, and so forth, were excluded from the study.

Written informed consent was obtained from all donors. The study was approved by the Local Ethics Committee of Baskent University (KA17/43).

2.1.1 | Measurements and definitions

The hemoglobinopathy analysis was performed using the high pressure liquid chromatography (HPLC) method.[15]

The results of the corrected QT interval (OTc), which was measured at every 30 minutes during the mobilization procedure, were also analyzed. The QT interval was estimated using Bazett's formula (QTc= QT: square root of RR interval). A QTc of >450 ms was accepted as QT prolongation.[16] Arterial blood pressure values measured from the right arm were defined as hypotension if the systolic blood pressure were <90 mm or if the diastolic blood pressure were <60 mm. Patients with CD34+ <10/L in peripheral blood at maximum stimulation were considered as "non-

TABLE 1 Baseline donor and cellular product characteristics of the donors with and without hemoglobinopathy

	Sickle cell trait subjects (*n*:11)	Control subjects (*n*:136)	*P* value
Age, year	36.0 ± 15.2	31.6 ± 15.2	.92
Gender (M/F)	5/6	77/59	.15
Weight, kg	71.8 ± 24.2	73.4 ± 13.8	.65
SBP before the procedure, mmHg	119 ± 11	126 ± 8	.60
DBP before the procedure, mmHg	73 ± 9	78 ± 6	.11
SBP after the procedure, mmHg	114 ±12	123 ± 8	.04
DBP after the procedure, mmHg	70 ± 6	75 ± 5	.02
Splenomegaly, %	2	0	N/A
Hemoglobin, g/dL	13.4 ± 1.1	13.8 ± 1.2	.60
WBC count, $\times 10^9$/L	48.4 ± 1.5	53.2 ± 20.7	.42
Platelet count, $\times 10^9$/L	237.2 ± 58.5	250.8 ± 73.6	.80
CD34+ cells in product, %	0.55 ± 0.27	0.85 ± 0.35	.04
CD 34+ cell count in product,/patient weight, kg	5.9 ± 3.5	9.2 ± 3.3	.11
TNC count in product,/patient weight, kg	10.93 ± 4.94	11.92 ± 3.95	.81
CD34+ cells in peripheral blood, %	0.15 ± 0.05	0.20 ± 0,12	.60
CD 34+ cell count in peripheral blood/μL	73.78 ± 28.88	112.05 ± 73.49	.51

DBP, diastolic blood pressure; F, female; M, male, SBP, systolic blood pressure; TNC, total nucleated cell count; WBC, white blood cell count.

mobilizers" and patients that did not harvest the minimal count of 2 × 106 CD34+/kg at maximum number of apheresis cycles were considered "poor mobilizers."[17]

2.2 | Stem cell mobilization and collecting procedures

All donors received 10 μg/kg/day filgrastim (Neupogen; Amgen-Roche, Thousand Oaks, CA) in two equal doses via the subcutaneous route for 4 days for mobilizing the stem cells from bone marrow into peripheral blood. Apheresis was performed using a Spectra Optia instrument (Terumo BCT; Lakewood, CO) according to the manufacturer's handbook, using standard-operating procedures (SOP; KIT-TU-003) compatible with the JACIE standards. According to the relevant SOP, anticoagulation was achieved through administration of Acid Citrate Dextrose-A (ACD-A) only at a ratio of 1:12 that of the inlet flow rate. Apheresis was performed until the total blood volume had been processed twice. The heart rate, ECG status, transcutaneous oxygen saturation level, and noninvasive blood pressure were monitored intermittently during each procedure. The donors were not given any supplements or drugs before the procedure.

2.3 | Statistical analysis

Statistical analysis was performed using SPSS software (Version 17.0, SPSS Inc., Chicago, IL). If continuous variables were normal, they were described as the mean ± standard

TABLE 2 Comparison of groups with regard to donor follow-up blood cell counts

	Hgb S trait subjects (*n*:11)	Control subjects (*n*:136)	*P* value
White blood cells ($\times 10^9$/L)			
Steady state	7.28 ± 1.99	8.89 ± 6.92	.9
1st week	7.14 ± 3.29	6.05 ± 0.86	.4
1st year	7.30 ± 1.53	5.88 ± 0.92	.03
Hemoglobin (g/dL)			
Steady state	13.55 ± 1.86	13.48 ± 1.41	.8
1st week	13.08 ± 2.05	13.15 ± 1.59	.9
1st year	13.69 ± 1.80	13.25 ± 0.99	.7
Platelet ($\times 10^9$/L)			
Steady state	241.24 ± 73.31	238.90 ± 43.76	.8
1st week	215.68 ± 80.25	184.40 ± 53.13	.2
1st year	243.76 ± 48.05	252.33 ± 72.32	1.0

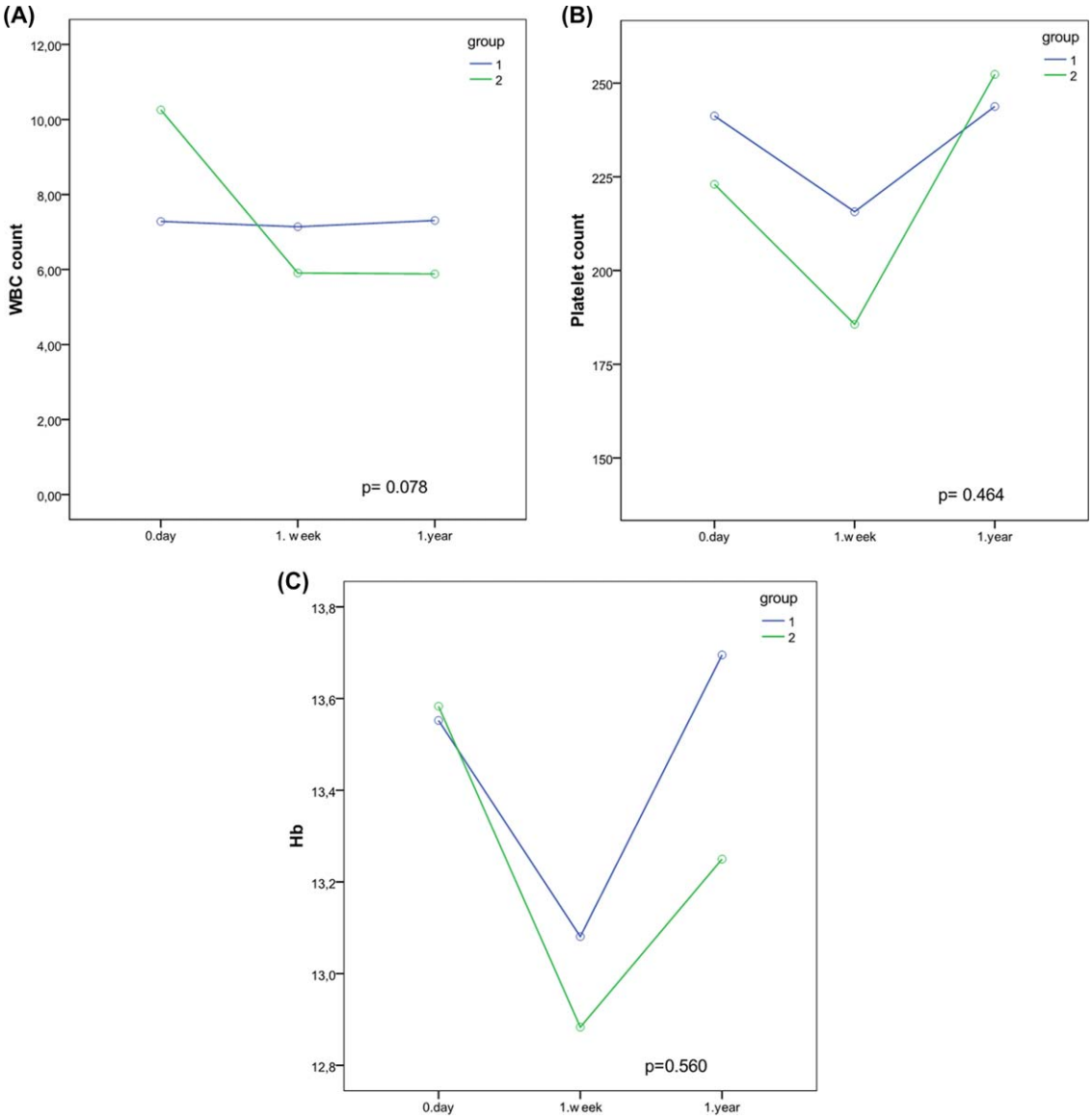

FIGURE 1 Linear modeling for comparison of A, WBC count; B, platelet count; and C, hemoglobin values of hemoglobin S trait donors and control subjects at baseline, 1th week and 1th year

deviation in Kolmogorov-Smirnov test or Shapira-Wilk, and if the continuous variables were not normal, they were described as the median. Comparisons between groups were applied using Mann Whitney *U* test for the data not normally distributed. Pre–post measures data were analyzed with Repeated Measure Analyses. The level for statistical significance was predetermined at $P < .05$.

3 | RESULTS

Eleven out of 147 (7.48%) donors were determined to be Hemoglobin S trait. All 147 donors could successfully complete G-CSF administration.

No significant difference was found between the groups with regard to age, gender and hematological parameters prior to the collecting procedure (Table 1).

The stem cell collecting procedure was completed successfully in both groups. Six (54.5%) donors in hemoglobin S trait group and 36 donors (26.4%) in control group underwent apheresis procedure twice. Mobilization failure or poor mobilization did not occur.

A statistically significant difference was detected between groups with regard to systolic and diastolic measurements after the procedure, however, the values were within normal ranges in both groups ($P = .04$ and $P = .02$).

The QTc values were within normal ranges during the apheresis procedure in both groups.

No difference was detected between groups with regard to CD34+ cell values. However, CD34+ cell percent in product was significantly higher in control group. The donor characteristics and stem cell characteristics in both groups have been presented in Table 1.

Several "typical" side effects were observed in donors with or without hemoglobinopathy. While 1 (9%) donor in hemoglobin S trait group and 3 (2%) donors in control group experienced paresthesia, 6 (54%) donors in hemoglobin S trait Group (1 required analgesic) and 64 (47%) donors in control group experienced bone pain (4 required analgesic), 2 (18%) donors in hemoglobin S trait group and 11 (8%) donors in control group experienced headache. In control group, one patient experienced nausea, 3 patients experienced dizziness, 1 patient experienced palpitation, 2 patients experienced abdominal pain, 3 patients experienced tetany resolving with oral calcium administration and 1 patient experienced atypical chest pain. No patients in each group experienced technical problems except one set-related problem in control group. No "unexpected" and "severe" side effects according to CTCAE were observed in both groups.

Ultrasonographic examination was performed in suspicion of splenomegaly on physical examination. Splenic enlargement was detected in two donors (150 mm at long axis for both) in hemoglobin S trait group. One donor in control group was suspected to have splenomegaly on physical examination, however, it was not verified on ultrasonography examination (Table 1).

When groups were compared with regard to steady state, 1st week and 1st year WBC, hemoglobin and platelet values, a difference was detected between groups with regard to 1st year WBC count ($P = .03$, Table 2), however, linear modeling revealed no difference between groups ($P = .078$) (Figure 1).

Gingival bleeding was detected 6 weeks after the cell collecting procedure in a healthy donor. No other late side effects were observed.

4 | DISCUSSION

Sickle cell disease is among the most common genetic diseases worldwide. Vaso-occlusive crises, hemolytic episodes, endothelial damage and inflammation caused by elevated cytokines are the characteristic clinical features of the disease.[12,18] These events result in organ damages and shorten the lifespan of the patients. The mean age of mortality is 39 years.[6,19] Cure may be achieved with HSCT. Although the vast majority of the patients had undergone the procedure using bone marrow, use of peripheral blood as the stem cell source has been increasing in adults in recent years.[12] This condition may lead to safety problems in Hemoglobin S trait sibling donors as it means exposure to G-CSF. Given that Hemoglobin S trait may occur in up to 13.6% of the population living in the Mediterranean region of Turkey[20] and the gradually increasing number of volunteer donors having registered to donor banks, not only related but also unrelated donors of SCD patients may be anticipated to be subjected to G-GCF.

Stem cell collecting from peripheral blood is a generally safe procedure. However, G-CSF-related early or late adverse events have rarely been reported in healthy donors.[21–24] Although last edition of FACT-JACIE standards (v.6.0) recommends hemoglobin electrophoresis for donor evaluation in endemic areas, the presence of Hemoglobin S trait status is not currently an exclusion criterion. Supporting this opinion, Panch et al. have found no severe adverse events associated with G-CSF administration and concluded that, Hemoglobin S trait donors could be eligible as unrelated donors in their study investigating the influence of race on stem cell mobilization.[25]

While systolic and diastolic blood pressures after the procedure were found significantly higher in control group, the values within normal ranges in both groups.

Ratio of the patients who underwent apheresis procedure twice was higher in hemoglobin S trait subjects. This was associated with lower CD34+ cell % in product in hemoglobin S trait group and higher target level of CD34+ cell in sickle cell patients.

G-CSF-related early adverse events are limited to bone aches, headache, and flu-like symptoms in healthy individuals.[26] Splenic rupture, vascular problems, and autoimmune abnormalities have been reported rarely.[23] In a prospective study conducted with 2408 unrelated peripheral blood donors registered in the National Marrow Donor Program (NMDP) between 1999 and 2004, toxicity was reported to be higher in female and obese donors. The overall grade III-IV toxicity rate was reported as 6% for healthy donors.[22] The Serious (Product) Events and Adverse Reactions Committee reported 79 events in 2014 including acute respiratory distress requiring intensive care unit follow-up after the third dose of G-CSF, and death from sudden cardiac failure during hiking 3.5 weeks after peripheral blood cell donation. The association with G-CSF could not be proven in the latter Case.[27] G-CSF-related temporal atypical inflammatory response presenting with fever, low back pain, lymphadenomegaly, and leukocytosis was reported in a healthy donor.[28]

Hematological parameters are within normal ranges in individuals with Hemoglobin S trait. However, these individuals are susceptible to some environmental conditions including strenuous sports such as fitness, insufficient fluid intake, alcohol use, and low oxygen pressure.[29] Individuals with Hemoglobin S trait are claimed to be under risk for thromboembolic events, rhabdomyolysis, cardiovascular system diseases, and sudden death.[8–11]

Al-Khabori and Kang reported a low side effect profile in 12 and 10 Hemoglobin S trait donors, respectively, and the side effect rates were not found to be different from those in healthy donors.[13,14] No mortality was reported. Our results

support these data. The mobilization procedure was found to be safe with regard to early complications. In our study, donors in both groups were observed to experience several typical side effects but no severe or unexpected side effects.

Mobilization with G-CSF is a generally safe procedure with regard to late side effects. There is no strong evidence hindering to perform the procedure safely. Asynchronous allele replication lasting for a couple of months and aneuploidy persisting for up to 268 days were reported as the late side effects in healthy donors.[30,31] Shapira reported DNA destabilization lasting for a few months.[32] DNA methyl transferase (DNMT) activity, which is known to increase in cancer patients, temporarily increases with G-CSF in healthy donors.[30] Benneth reported non-Hodgkin's lymphoma in 3 out of 538 donors 1–5 years after the mobilization procedure and acute myeloid leukemia in 2 out of 200 donors and stressed the necessity of long-term follow-up of donors, although he did not prove the causality.[26] WMDA reported 16 malignancies (3 hematological malignancies), 4 autoimmune events and also allergic, cardiac, gastrointestinal events, and infections as the late adverse events.[27]

There is evidence on the susceptibility to some autoimmune events and cancer among individuals with Hemoglobin S trait.[33,34] G-CSF-related late complications have not been reported until today. We did not detect significant late complications in our cases. However, the literature data is limited on the donor follow-up, because donor follow-up is not undertaken in most transplant centers. Therefore, developing policies for regular follow-up of Hemoglobin S trait donors is of great importance.

5 | CONCLUSION

G-CSF may be used safely in hemoglobin S carriers who are volunteers for being donors. This result has significance as the rate of hemoglobin S carriers may be high among donors of SCD patients, and carrier subjects being eligible as donors due to safety of G-CSF would increase the chance of the patients for allogeneic stem cell transplantation. Close follow-up of HbS trait donors has vital importance for better understanding these issues. Further studies are required to reveal the safety profile of G-SCF in hemoglobin S carriers in different regions.

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